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Translational Article

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Translational

Frailty Status and Altered Glucose-Insulin Dynamics

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Background. We examined women in their 80s and 90s and evaluated the hypothesis that abnormalities in the dynamic response of glucose and insulin to a glucose load are associated with frailty status.

Methods. We performed a 75 g oral glucose tolerance test in 73 community-dwelling women aged 84–95 years without known diabetes enrolled in the Women's Health and Aging Study II. We examined the association of frailty status (nonfrail, prefrail, or frail) with oral glucose tolerance test glucose and insulin levels at 0, 30, 60, 120, and 180 minutes using multiple linear regression models.

Results. Using American Diabetes Association criteria, only 27% of older women had normal glucose status, 48% had prediabetes, and 25% had undiagnosed diabetes. Fasting glucose, fasting insulin, homeostasis model of assessment-insulin resistance, and Matsuda index were similar by frailty status, adjusting for age and body mass index. Conversely, mean oral glucose tolerance test glucose levels were higher at 60 minutes (44.6 ± 18.1 mg/dL higher) and 120 minutes (67.1 ± 23.5 mg/dL higher) and to a lesser extent at 180 minutes (44.3 ± 22.5 mg/dL higher) in frail versus nonfrail women as was integrated glucose area after adjustment. Mean 120-minute insulin level was also higher in frail versus nonfrail women (45.7 ± 22.4 μU/mL higher). Overall, glucose and insulin responses were more exaggerated and prolonged in frail versus nonfrail or prefrail women.

Conclusions. Our data demonstrate dysregulation in response to glucose challenge as a component of physiologic vulnerability associated with frailty in old–old women. Future studies should examine the timing of abnormal glucose–insulin dynamics with respect to the pathogenesis of frailty.

Key Words: Glucose—Insulin—Dynamics—Elderly—Frailty.

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Aging is associated with a decrease in insulin sensitivity and elevated levels of glucose, particularly after oral glucose challenge testing (1,2). As a result, older individuals are more likely to be classified as "abnormal" compared with younger adults using similar diagnostic criteria for diabetes (3,4). However, studies that demonstrate preserved insulin action in healthy centenarians compared with younger adults dispute the notion that abnormal glucose status is an unavoidable companion to aging (5). Instead, older adults with abnormal glucose status may represent a vulnerable subset at high risk for adverse outcomes. This is supported by results from the Baltimore Longitudinal Study of Aging demonstrating higher mortality in older adults with impaired glucose states (2).

Frailty is a clinical syndrome distinguished by a characteristic phenotype, increased vulnerability to stressors, and a high risk of adverse outcomes, including disability, hospitalization, and death (6,7). In the general population, frailty increases with age, with a prevalence of more than 25% in those older than 85 years (6).

The presence of diabetes is associated with frailty status, with increasing prevalence of diabetes noted in frail, and to a lesser extent prefrail, compared with nonfrail adults (8). The classification of prediabetes by frailty status has not been specifically examined in previous studies. However, a few studies suggest both cross-sectional and longitudinal associations between high glucose and/or insulin levels, even within the nondiabetic range and frailty (8–11). Yet, most studies characterizing these associations have focused on fasting levels, whereas it is theorized that the dynamic response to a glucose challenge may better identify frail from nonfrail individuals

and give insight into frailty as a syndrome of decreased physiologic reserve (12). The one study that examined associations of 2-hour values with frailty (8) was not able to characterize the dynamic response of glucose and insulin across a range of time points following a glucose challenge or, as a result, adequately establish whether frail adults without known diabetes are more likely to have insulin resistance versus insulinopenia underlying the observed hyperglycemia, although fasting indices have suggested insulin resistance (11).

In the present study, we sought to determine the association of abnormal glucose status (prediabetes and diabetes) with frailty in women in their 80s and 90s. We also aimed to examine whether oral glucose tolerance test (OGTT) glucose and insulin responses were independently associated with frailty status in old–old women without a known diagnosis of diabetes. Our hypotheses were as follows: (a) Frail older women have a higher prevalence of abnormal glucose status compared with prefrail and nonfrail women, (b) altered dynamic responses of glucose and insulin during OGTT are more strongly associated with frailty status compared with fasting values, and (c) frail women are characterized by relative insulin resistance.

METHODS

Participants

Study participants were community-dwelling women who had enrolled in 1994 in a longitudinal population-based study, the Women's Health and Aging Study II (7). Women aged 65 years and older were originally recruited from a random sample selected from the Health Care Financing Administration's Medicare Eligibility list for Baltimore, MD. Women aged 70–79 years with difficulty in zero or one of four domains of physical function were eligible for Women's Health and Aging Study II; 436 women representative of the two thirds least disabled older women living in the community enrolled. Standardized evaluations, interviews, and physical examinations were conducted at the Johns Hopkins Functional Laboratory during seven study visits from 1994 to 2008. At the seventh study visit, participants were invited to participate in a home substudy visit in which standard OGTTs were performed. These substudy visits occurred from May 2008 to March 2009. Women with a history of diagnosed diabetes or taking corticosteroids were ineligible for the glucose tolerance test, yielding 73 study participants.

The Johns Hopkins University Institutional Review Board approved the study, and all participants gave informed consent.

Biochemical Measurements

Serum samples were collected after a 12-hour fast (Time 0), followed by oral administration of 75 g of glucose (Fisher Healthcare). Additional serum samples were collected at 30, 60, 120, and 180 minutes. All samples were processed on site in a refrigerated centrifuge, transported on ice, and stored at –80ºC for batched analysis. Glucose was measured using the glucose oxidase method on a Beckman Glucose Analyzer 2 (Beckman Diagnostics, Fullerton, CA), with intra-assay and inter-assay coefficients of variation of 1.38% and 1.52%, respectively. Insulin was measured by radioimmunoassay (Linco Research Inc., St. Louis, MO), with an assay sensitivity of 2 μU/mL and intra-assay and inter-assay coefficients of variation of 4.42% and 5.95%, respectively.

Diabetes Classification

Diabetes classification in women without known diabetes was performed using American Diabetes Association (4) criteria based on fasting glucose greater than or equal to 126 mg/dL and/or 2-hour glucose greater than or equal to 200 mg/dL. Prediabetes was classified based on the presence of isolated impaired fasting glucose (fasting glucose 100–125 mg/dL), isolated impaired glucose tolerance (2-hour glucose 140–199 mg/dL), or both.

Frailty Status

Frailty status was assessed at the seventh round and was defined as originally operationalized by Fried and colleagues (6) in the Cardiovascular Health Study (CHS) and validated by Bandeen-Roche and colleagues (7) in the Womens Health and Aging Study studies. Five criteria were used: shrinking (body mass index [BMI] < 18.5 kg/m^2 or 5% annual weight loss), weakness (grip strength equivalent to the lowest quintile in CHS, by gender and BMI strata), poor endurance (self-reported exhaustion), slowness (walking speed equivalent to the lowest quintile in CHS, by gender and height strata), and low activity (activity level in kilocalories per week equivalent to the lowest quintile in CHS, by gender). Those with zero criteria were categorized as nonfrail, those with one to two criteria as prefrail, and those with more than three criteria as frail.

Statistical Analysis

Baseline characteristics were compared by frailty status using the chi-squared test for binary outcomes and Student's *t* tests for continuous outcomes. Insulin resistance was estimated by the homeostasis model of assessment-insulin resistance (HOMA-IR), calculated using the following equation: fasting glucose (mg/dL) × fasting insulin (uU/mL)/405 (13). Whole-body insulin sensitivity was estimated using the Matsuda index, calculated as 10,000/square root of ([fasting glucose × fasting insulin] × [mean glucose × mean insulin during OGTT]), which provides a good approximation of measurements obtained by the euglycemic insulin clamp technique (14). Integration of the glucose and insulin OGTT curves (ie, area under the curve [AUC]) was calculated by the standard trapezoid method using participants with measurements at all time points (n = 68 for glucose AUC and n = 69 for insulin AUC).

We performed multiple linear regression analyses, adjusting for age and BMI, to examine the relationship between frailty status (nonfrail, prefrail, and frail) and OGTT glucose and insulin measures at 0, 30, 60, 90, 120, and 180 minutes. Beta coefficients (± standard error) are reported. Robust regression models were also examined and compared with linear regression models. The robust regression method accounts for the presence of potential outliers in the outcome variable (15). In brief, this analysis uses the median of the squared residuals instead of the sum of the

Table 1. Demographic and Clinical Characteristics of Women by Frailty Status, WHAS II

	All (n = 73)*	Nonfrail (n = 17)*	Prefrail (n = 47)*	Frail (n = 9)*	p Value†
Age (years)	86.7 ± 0.3	86.7 ± 0.7	86.8 ± 0.4	86.2 ± 0.5	.64
White (%)	84.9	82.4	87.2	77.8	.78
Education (years)	13.1 ± 0.3	13.5 ± 0.8	13.1 ± 0.4	12.4 ± 0.6	.56
BMI (kg/m^2)	26.4 ± 0.6	24.5 ± 0.6	26.7 ± 0.8	28.4 ± 1.6	.01
Osteoarthritis (%)	42.5	23.5	44.7	66.7	.08
CHD (%)	28.8	11.8	31.9	44.4	.09
Hypertension (%)	48.0	47.1	42.6	77.8	.10
Cancer (%)	26.0	35.3	19.2	44.4	.24
COPD (%)	31.5	35.3	27.7	44.4	.61
Glucose (mg/dL)					
Fasting	96.5 ± 1.7	96.4 ± 3.4	94.9 ± 1.9	101.6 ± 6.5	.60
30 min	155.9 ± 3.6	162.7 ± 7.8	151.0 ± 3.7	163.8 ± 15.1	.32
60 min	175.9 ± 5.5	166.5 ± 13.4	170.3 ± 4.9	212.2 ± 19.7	.11
120 min	168.5 ± 7.3	155.3 ± 15.2	160.2 ± 7.2	222.9 ± 23.4	.04
180 min	119.2 ± 6.5	117.2 ± 13.2	111.4 ± 5.8	159.9 ± 31.2	.30
Integrated area (mg min^{-1} dL^{-1})	27,725 ± 889	26,964 ± 2,029	26,661 ± 831	34,160 ± 3,609	.14
Insulin (μU/mL)					
Fasting	12.4 ± 0.7	12.1 ± 1.4	12.1 ± 0.7	14.3 ± 2.9	.75
30 min	67.7 ± 5.9	74.2 ± 12.5	62.3 ± 7.3	68.8 ± 15.1	.69
60 min	83.9 ± 7.0	73.8 ± 11.5	78.0 ± 8.0	113.2 ± 26.1	.38
120 min	91.4 ± 7.1	85.0 ± 13.0	78.8 ± 6.2	143.4 ± 33.0	.16
180 min	39.6 ± 3.9	38.7 ± 6.3	36.7 ± 4.6	55.1 ± 16.4	.56
Integrated area (μU min^{-1} mL^{-1})	12,664 ± 842	12,487 ± 1,439	11,689 ± 890	17,628 ± 3,796	.31
HOMA-IR units‡	3.0 ± 0.2	2.9 ± 0.4	2.8 ± 0.2	3.6 ± 0.7	.63
Matsuda index§	3.5 ± 0.2	3.4 ± 0.3	3.8 ± 0.3	2.6 ± 0.5	.12

Notes: BMI = body mass index; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; HOMA-IR = homeostasis model of assessment-insulin resistance; OGTT = oral glucose tolerance test; WHAS II = Women's Health and Aging Study II.

*Unless otherwise indicated, mean (±*SE*) are reported.

†p Value indicates differences by frailty status.

‡Calculated as (fasting glucose × fasting insulin)/405.

§Calculated as 10,000/square root ([fasting glucose × fasting insulin]/[mean glucose × mean insulin during OGTT]).

squared residuals. We also performed sensitivity analyses excluding women with undiagnosed diabetes.

Results

The mean age of study participants was 86.7 years (range 84–95 years) as shown in Table 1. Frail women had a higher mean BMI than prefrail and nonfrail women (28.4, 26.7, and 24.5 kg/m^2, respectively). Frail women also had a higher prevalence of chronic diseases such as osteoarthritis, coronary heart disease, hypertension, cancer, and chronic obstructive pulmonary disease compared with prefrail and nonfrail women, although the differences were not as large.

Only 27% of study participants had normal fasting glucose (<100 mg/dL) and normal glucose tolerance (2-hour glucose <140 mg/dL), whereas 48% had prediabetes, defined as impaired fasting glucose, impaired glucose tolerance, or both, and 25% had undiagnosed diabetes (Table 2). The high prevalence of both prediabetes and diabetes was largely due to having an abnormal OGTT, with 71% of those with prediabetes and 78% of those with diabetes achieving these diagnoses exclusively due to presence of a high 2-hour glucose level.

When the prevalence of each diabetes classification was examined by frailty status, none of the frail women had both

Table 2. Prevalence of Normal Glucose Status, Prediabetes, and Diabetes Using ADA Criteria by Frailty Status*

		Frailty Status		
Glucose Status	All	Nonfrail	Prefrail	Frail
Normal	20 (27)	5 (29)	15 (32)	0 (0)
Prediabetes	35 (48)	10 (59)	21 (45)	4 (44)
Only fasting glucose 100–125 mg/dL (IFG)	*1 (3)*	*0 (0)*	*1 (5)*	*0 (0)*
Only 2-h glucose 140–199 mg/dL (IGT)	*25 (71)*	*6 (60)*	*16 (76)*	*3 (75)*
Both IFG and IGT	*9 (26)*	*4 (40)*	*4 (19)*	*1 (25)*
Diabetes	18 (25)	2 (12)	11 (23)	5 (56)
Only fasting glucose ≥126 mg/dL	*1 (5)*	*0 (0)*	*1 (9)*	*0 (0)*
Only 2-h glucose ≥200 mg/dL	*14 (78)*	*1 (50)*	*9 (82)*	*4 (80)*
Both	*3 (17)*	*1 (50)*	*1 (9)*	*1 (20)*
Total	73 (100)	17 (100)	47 (100)	9 (100)

Notes: Italics indicate subcategory values. ADA = American Diabetes Association; IFG = impaired fasting glucose; IGT = impaired glucose tolerance.

*Both n and (%) shown above. Percentage calculated within each category (column) of frailty status, then within each diabetes classification.

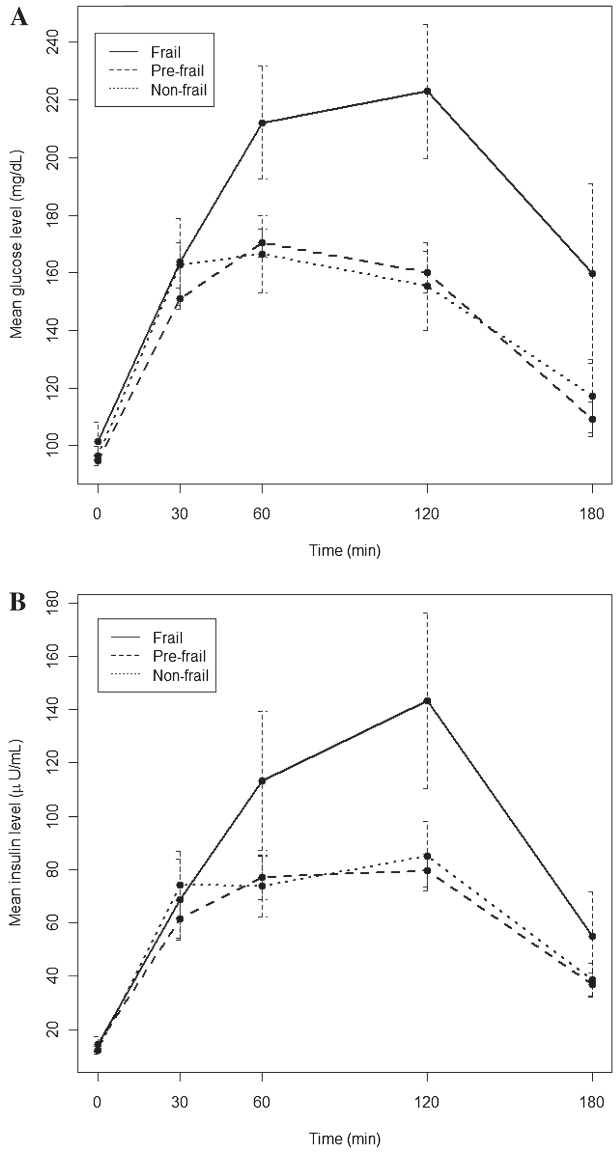

Figure 1. Glucose and insulin dynamics during oral glucose tolerance test by frailty status. (**A**) and (**B**) show mean ± *SE* (error bars) for glucose and insulin values, respectively, at 0, 30, 60, 120, and 180 minutes after a 75 g glucose load by frailty status.

normal fasting and 2-hour values; all were classified as having either prediabetes or diabetes. In addition, the prevalence of diabetes increased in a stepwise fashion by frailty status, with 12% of nonfrail, 23% of prefrail, and 56% of frail women classified as having diabetes.

We subsequently examined the average glucose and insulin dynamics during OGTT by frailty status. After 75 g oral glucose challenge (Figure 1A), the frail group exhibited altered glucose dynamics, with both a delayed and higher peak and prolonged glucose levels relative to both the prefrail and the nonfrail groups. As shown in Figure 1B, the insulin dynamics largely paralleled those of glucose, with a more distinct and higher peak and prolonged insulin levels relative to prefrail and nonfrail groups. These findings were consistent with our a priori hypotheses of altered glucose–insulin dynamics in frail women.

Mean fasting glucose and insulin values did not differ by frailty status (Table 1 and Figure 1). Conversely, OGTT glucose levels at 120 minutes were higher in frail (222.9 ± 23.4 mg/dL) versus prefrail (160.2 ±7.2 mg/dL) and nonfrail (155.3 ± 15.2 mg/dL) women, whereas glucose levels at 60 and 180 minutes were also higher but differences were not as large. OGTT insulin levels were higher in frail women compared with their counterparts at 60, 120, and 180 minutes as was integrated glucose area, integrated insulin area, and HOMA-IR, but these differences were not large. Although insulin sensitivity as assessed by Matsuda Index was lowest in frail women, the differences were not large compared with nonfrail and prefrail women.

In linear regression analyses adjusted for age and BMI, fasting and 30-minute glucose levels did not differ between frail and nonfrail women (Table 3). In contrast, glucose levels were higher at 60 minutes (44.6 ± 18.1 mg/dL higher) and 120 minutes (67.1 ± 23.5 mg/dL higher) and to a lesser extent at 180 minutes (44.3 ± 22.5 mg/dL higher) in frail versus nonfrail women. Glucose AUC was also higher (7128 ± 3009 mg min^{-1} dL^{-1} higher) in frail versus nonfrail women. No "large" differences were noted between prefrail and nonfrail women in glucose levels at 0, 30, 60, 120, or 180 minutes or glucose AUC.

In linear regression analyses adjusted for age and BMI, fasting insulin levels did not differ between frail and nonfrail women (Table 3). Conversely, insulin levels were higher at 120 minutes (45.7 ± 22.4 μU/mL higher) in frail versus nonfrail women, whereas other OGTT insulin measurements, insulin AUC, HOMA-IR, and Matsuda index did not differ greatly between frail and nonfrail women. No differences were noted between prefrail and nonfrail women for insulin levels at any time point or insulin AUC.

In age- and BMI-adjusted robust regression analyses, 120-minute glucose levels remained higher in frail versus nonfrail women (55.5 ± 21.8 mg/dL higher) as they did in adjusted sensitivity analyses excluding women with undiagnosed diabetes (47.7 ± 20.5 mg/dL higher).

Discussion

Our data demonstrate that the prevalence of prediabetes (48%) and undiagnosed diabetes (25%) is extremely high in old–old women, largely manifested as an abnormal 2-hour OGTT glucose value. We also report that frailty was most strongly associated with the 2-hour OGTT glucose value in these women, robust even in sensitivity models, suggesting clinical meaningfulness to this testing abnormality. Our data support the value of glucose challenge testing to distinguish between physiologically frail women and their nonfrail or prefrail counterparts when basal unchallenged levels do not.

The high prevalence of prediabetes and diabetes in our study is consistent with nationally representative estimates

Table 3. Association of Frailty Status With OGTT Glucose (mg/dL) and Insulin Measurements (μU/mL)*

		0 min	30 min	60 min	120 min	180 min	AUC†	HOMA-IR	Matsuda Index
Glucose	Nonfrail	Reference	Reference	Reference	Reference	Reference	Reference	—	—
	Prefrail	−2.2 ± 4.0 (p = .58)	−13.5 ± 8.6 (p = .12)	1.8 ± 12.3 (p = .88)	3.2 ± 16.0 (p = .84)	−5.3 ± 15.7 (p = .74)	−481 ± 2,092 (p = .82)	—	—
	Frail	5.1 ± 5.8 (p = .38)	−0.8 ± 12.7 (p = .94)	44.6 ± 18.1 (p = .02)	67.1 ± 23.5 (p = .006)	44.3 ± 22.5 (p = .054)	7,128 ± 3,009 (p = .02)	—	—
Insulin	Nonfrail	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Prefrail	−1.2 ± 1.5 (p = .43)	−22.3 ± 12.9 (p = .09)	−7.2 ± 15.0 (p = .63)	−14.2 ± 15.3 (p = .36)	−4.3 ± 9.6 (p = .65)	−2,114 ± 1,887 (p = .26)	−0.4 ± 0.4 (p = .36)	0.7 ± 0.5 (p = .14)
	Frail	0.2 ± 2.3 (p = .93)	−24.7 ± 19.0 (p = .20)	23.0 ± 22.0 (p = .30)	45.7 ± 22.4 (p = .045)	11.8 ± 13.8 (p = .40)	2,975 ± 2,684 (p = .27)	0.2 ± 0.6 (p = .79)	−0.3 ± 0.7 (p = 0.66)

Notes: AUC = area under the curve; HOMA-IR = homeostasis model of assessment-insulin resistance; OGTT = oral glucose tolerance test.
*Beta coefficients (±*SE*) are shown. All analyses are adjusted for age and body mass index.
†Units for glucose AUC are mg min^{-1} dL^{-1} and for insulin AUC are mU min^{-1} mL^{-1}.

(3). Overall, men and women aged 75 years and older in the United States have a similar prevalence of prediabetes (46.8%), though a lower prevalence of undiagnosed diabetes (13.4%), compared with our study. One explanation for the higher prevalence of undiagnosed diabetes in our study is the inclusion of frail individuals who ordinarily exclude themselves from research studies. Similar to our findings, the 2-hour OGTT glucose level was better able to identify older participants with undiagnosed diabetes than the fasting glucose level in national surveys (3). These data suggest that our high prevalence of abnormal 2-hour OGTT glucose levels was not simply due to high prior rates of fasting glucose screening by the participants' physicians. Data from the Baltimore Longitudinal Study of Aging also demonstrate an age-related increase in progression rate from normal glucose status to impaired glucose tolerance but not from normal glucose status to impaired fasting glucose (16). Thus, greater OGTT testing would lead to a high prevalence of previously unrecognized prediabetes and diabetes in the older adults.

Aging is associated with impaired insulin sensitivity, with greater elevations seen in 2-hour glucose OGTT glucose values compared with fasting levels, although the presence of age-related differences in insulin secretion remains unclear (1,2,17–19). Several studies further propose that the additional diabetes cases detected with OGTT in older adults are clinically relevant. In Baltimore Longitudinal Study of Aging, the 2-hour OGTT glucose was associated with better mortality risk prediction than fasting glucose alone (2,20) with similar findings in CHS with respect to incident cardiovascular events (21). Taken together, these data suggest that the 2-hour glucose level predicts adverse events in older people and may warrant the additional inconvenience of OGTT administration.

Our findings of frailty being associated with higher 2-hour OGTT glucose levels in individuals without diabetes are consistent with those from CHS in which frailty was associated with the 2-hour, but not the fasting, glucose level in men and women without diabetes (8). Few other studies have investigated associations between abnormal glucose status and frailty. Hyperglycemia, measured by hemoglobin A1c, is associated with a higher likelihood of frailty (9). Insulin resistance is associated with incident frailty; for every standard deviation increment in HOMA-IR, the adjusted hazard ratio for frailty was 1.15 (95% *CI*: 1.02–1.31) (10). Individuals who eventually developed frailty were also more likely, in parallel, to develop diabetes compared with older adults who never developed frailty (8.6% vs 4.2%). Thus, the association between frailty and abnormal glucose status may be bidirectional though more longitudinal studies are needed.

The underlying physiological mechanisms relating frailty and abnormal glucose status are not fully understood. One hypothesis is that inflammatory pathways may be the link. Frail older adults have a higher burden of

inflammatory markers (8), which are also associated with insulin resistant states (22). An alternative hypothesis is that the conditions are related through a primary defect in muscle metabolism. In older adults, skeletal muscle protein synthesis may be resistant to the anabolic action of insulin (23). Insulin resistance is also associated with activation of muscle proteolysis (ie, ubiquitin) pathways (24). Both processes likely contribute to the muscle loss inherent in the frailty phenotype. In turn, reduced muscle surface area for insulin-mediated glucose uptake may then aggravate peripheral insulin resistance, leading to a vicious cycle. Furthermore, elevated inflammatory markers are also associated with muscle loss (25). Thus, insulin resistance, inflammation, and muscle loss may represent related processes that manifest as the phenotype of frailty in a vulnerable subset of older adults.

Altered glucose dynamics in frailty was previously described in frail older adults who underwent a meal test and had a more exaggerated and prolonged glucose response after 2 hours compared with nonfrail older adults (26). We observed a more exaggerated and prolonged response for both glucose and insulin in our study. The meal test contains 32 g of carbohydrate and is likely not as potent a stimulus as the 75 g offered in our study.

Although surrogate indices of insulin sensitivity (Matsuda) and resistance (HOMA-IR and insulin AUC) were not statistically significantly different by frailty status, the exaggerated insulin dynamics observed in our study support the presence of insulin resistance in frailty. Interestingly, one study found that only frail obese, but not frail lean adults, had reduced insulin sensitivity versus nonfrail counterparts (11). In contrast, although the frail women in our study had higher mean BMI, we still found significantly higher 2-hour insulin levels in frail women compared with their counterparts in adjusted analyses. Our results suggest that altered glucose–insulin dynamics in frailty are independent of differences in BMI.

To our knowledge, this is the largest study of oral glucose tolerance testing in women older than 80 years that also investigates associations with frailty status. We were uniquely able to include women of this age group for our study because of the commitment they had already demonstrated to the Women's Health and Aging Study II study, sustained for more than 15 years, and the use of home visits. However, limitations to our study include the number of study participants. The frail women composed a relatively small subgroup, which may affect our ability to discern statistically significant differences, for instance, in the prevalence of chronic comorbidities by frailty status, although observed differences could be clinically meaningful. Consequently, confirmation of our findings in other studies is needed. Other limitations include performance in women only, limiting our ability to generalize to frailty in men, and the cross-sectional nature of our data, which limits inferences on temporality.

In summary, our study has both clinical and physiologic implications. From the clinical standpoint, our data build on existing literature to suggest that higher 2-hour glucose levels, even within the nondiabetic range, are associated with adverse consequences in older persons. From the physiologic standpoint, we provide the first evidence that glucose–insulin dynamics after OGTT (vs fasting levels) are different in frail women compared with their counterparts, supporting the notion that challenge testing may best identify individuals with decreased physiological reserve. Future studies should examine the timing and relationship of these glucose–insulin abnormalities with respect to the pathogenesis of frailty, as well as their associations with dysregulation in other physiologic systems.

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